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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,166	11/17/2000	Douglas A. Treco	10278-014001	6951

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EXAMINER
JIANG, DONG

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/716,166	Applicant(s) TRECO ET AL.	
	Examiner Dong Jiang	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-83* is/are pending in the application.

4a) Of the above claim(s) *16 and 53-82* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,17-52 and 83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3 & 4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED OFFICE ACTION

Applicant's election with traverse of Group I invention, claims 1-15, 17-52 and 83, in Paper No. 7, filed on 10 June 2002 is acknowledged. The traversal is on the ground(s) that groups I and II are different only in the source of the nucleic acid sequence encoding a small polypeptide in the claimed cells, that the fact that the source of the nucleic acid sequence can be an endogenous or exogenous nucleic acid sequence does not make the restriction groups independent or distinct under the proper standard, and that there is no evidence that groups I and II would have a separate status in the art or a different field of search as they are under the same classification. This is not found persuasive because the techniques, reagents and cells required for the expression of an endogenous sequence and an exogenous sequence are different, therefore, the two groups have acquired a separate status in the art as shown by their recognized divergent subject matters, even though they are under the same classification. Further, a search for one group may reveal overlapping information about the other group, however, a search is aimed to find references which would render the invention obvious, as well as references directed to anticipation of the invention. As such, a search for one group is not adequate as to revealing references anticipating the other groups. Thus, independent searches of relevant literature in different areas of subject matter are required for different groups.

The requirement is still deemed proper and is therefore made FINAL.

Applicant's species election of GLP-1 and furin in Paper No. 10 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Currently, claims 1-83 are pending, and 1-15, 17-52 and 83 are under consideration.

Applicants submission of IDS references listed on PTO-1449, paper No. 4, is acknowledged. It is noted that the relevance of references AR-AT cannot be assessed as the references are amino acid sequences, and no indication of relevance or alignment to the disclosed sequences has been provided.

Formal Matters:

Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are directed.

Claims

Claims 1, 5, 28, 34 and 52 are objected to for the following informalities, appropriate correction is required for each item:

Claim 1, line 1, the "A ... constructs" should be "A ... construct"; and "for expression a small ..." should be "for expression *of* a small ...". Further, "a functional fragment *of* analog" should read "a functional fragment *or* analog"

Claim 5, the word "exendid" should be "exendin".

Claim 28, line 1, the word "form" should be "from".

Claim 34, line 1, the second "is" is not needed.

Claim 52, the word "methods" should be "method".

Objections and Rejections under 35 U.S.C. 112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15, 17-52 and 83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 14 are indefinite for the recitation of "a functional fragment of analog". It is unclear what function is referred to.

Claim 2 is indefinite for the recitation of "the nucleic acid sequence ... is from the pro-region" as the term "pro-region" is used to specify an amino acid sequence. Similar indefiniteness is found throughout the claims, for example, claims 6, 7, 17, 18, 28, 45, 47 and 51. Applicant is required to amend all claims pertaining to this matter.

Claim 6 is further indefinite as it is unclear what "a site" is for, i.e., whether "a site" is for various protein modifications, or for peptide cleavage, or merely a location. The metes and bounds of the claim, therefore, cannot be determined. Claim 17 is similarly indefinite.

Claim 8 is indefinite because "the site" is a part of the construct, which is a nucleic acid according to the independent claim, thus "the site" cannot be cleaved by proteases. Claim 32 is similarly indefinite.

Claim 9 is indefinite because it is unclear what is meant by "end protease cleavage site" as the site is located within a peptide sequence according to the limitation in the independent claim, or whether "endoprotease cleavage site" is intended.

Claim 14 is further indefinite for failing to specify the relationship between elements. It is unclear how the exogenous nucleic acid sequence is related to the nucleic acid sequence encoding the small peptide, and whether the cell produces the small peptide is the result of introducing the exogenous nucleic acid sequence, or cell produces the small peptide regardless. Claim 15 is similarly indefinite.

Claim 17 is further indefinite because it is unclear what is intended by "the *cell* further comprises a *site*".

Claims 19 and 39 are indefinite for the recitation of "mature form". A mature form of a peptide varies depending upon the cell type used to express the peptide. As such, the metes and bounds of the claim cannot be unambiguously determined.

Claim 36 recites the limitation " *the* cleavage site " in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 41 is indefinite because there are two "a small peptide" in the claim, and it is unclear whether they are intended to be the same peptide. The word "the" or "said" is suggested for the second "a" small peptide if the same peptide is indicated.

Claim 47 is further indefinite for the recitation of "nucleic acid sequence which comprises the pro-region" as the term "pro-region" is used to specify an amino acid sequence. "Encodes" is suggested to replace "comprises". Additionally, it is unclear whether the nucleic acid sequence encoding the pro-region is liked to the nucleic acid encoding the small peptide prior to the "introducing", or as a result of.

Claim 83 is indefinite because there is no structural relationship between the elements.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claim 15 is directed to a cell comprising an exogenous nucleic acid sequence encoding the prepro-region of somatostatin and an endogenous nucleic acid sequence encoding a small peptide. However, neither the claim, nor the specification provides specific information as to how the exogenous and the endogenous sequences are related, and how one affect the other regarding the expression of the small peptide. Additionally, the specification provides no guidance, or working example as to how to make such a cell. As such, one of skill in the art would not know how to make the invention, and undue experimentation is required prior to using the claimed invention.

Due to the large quantity of experimentation necessary to determine how to make the claimed cell, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, undue experimentation would be required of the skilled artisan to make the claimed invention.

Claim 15 is further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 15 is directed to a cell comprising an exogenous nucleic acid sequence encoding the prepro-region of somatostatin and an endogenous nucleic acid sequence encoding a small peptide. However, no such cell meeting the limitations of the claim is identified or particularly described in the specification.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. As the specification does not provide adequate written description as to such cell, which would express the small peptide, the conception is not achieved until reduction to practice has occurred. One cannot describe what one has not conceived. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6-10, 12, 14, 17-20, 22, 23, 26-30, 32-34, 38-41, and 43-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Sevarino et al. (Cell, 1989, 57(1): 11-19, provided by the applicants).

Sevarino discloses a vector (page 16, the right column, and page 18, the left column) for the expression of a hybrid protein, which comprises the leader sequence and a portion of the pro-

region of the rat preprosomatostatin (rPPSS) and a small heterologous peptide, which is the carboxyl terminal portion of the anglerfish preprosomatostatin-2 (a(II)PPSS). Sevarino further teaches when transfected cells with said vector, a mature form the small peptide was produced. The referenced vector, therefore, anticipates claims 1-3 and 12 as being a nucleic acid construct comprising at least one regulatory sequence, and encoding the pre-region and the pro-region of a somatostatin, and a small peptide hormone. With respect to claim 4, somatostatin is considered "an anti-diabetic peptide", as the prior art acknowledges that somatostatin can be used, in conjunction with insulin, to treat diabetic ketoacidosis (see the cited reference below). Therefore, the reference also anticipates claim 4. Additionally, the referenced construct comprises a cleavage site between the sequences encoding the pro-region and the small peptide, thus, anticipates claims 6 and 7. With respect to claims 8 and 9, although the reference is silent on whether the cleavage site is a multibasic, dibasic, or monobasic site, the reference still anticipates the claim because the claim limitation covers all possible types of cleavage sites one can generate. With respect to claim 10, although the reference does not specify a pro-protein convertase responsible for generating the mature form of the peptide, the fact that the construct is made in such a way to encode a pro-protein, and that a mature form of the peptide is made from the construct, confirms the involvement of a pro-protein convertase. As such, the reference anticipates claim 10.

Further, Sevarino teaches (page 16, the right column) a mouse corticotrophic AtT20 cell, and a rat RIN 5F insulinoma cell transfected with said vector (as claims 14, 17-20, 22, 23, 26-30, 32-34), a method of making a small peptide by culturing the transfected cells, which produce mature somatostatin peptide (as claims 38-40), and a method of making a cell expressing the small peptide by transfecting said cells with the nucleic acid construct (as claims 41 and 43-45), thus anticipates claims 14, 17-20, 22, 23, 26-30, 32-34, 38-41, and 43-45.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5, 9, 11, 13, 31, 35, 37, 46, 52 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sevarino et al. (Cell, 1989, 57(1): 11-19) as applied to claims 1-4, 6-8, 10, 12, 14, 17-20, 22, 23, 26-30, 32-34, 38-41, and 43-45 above, and further in view of Stoller et al. (J. Cell Biol., 1989, 108: 1647-55, provided by applicants), Habener et al. (US 5,118,666), Suzuki et al. (US 5,891,671), and Patel et al. (CIBA Foundation Sumposium, 1995, 190: 26-50).

The teachings of Sevarino are reviewed above. From the experimental result, the reference further indicates that the pro-region sequences are critical in defining correct intracellular sorting of the somatostatin precursors. The primary reference does not teach a construct comprising nucleic acid sequences encoding the prepro-region of a preprosomatostatin and GLP-1 peptide.

Stoller teaches an expressing vector comprising nucleic acid sequences encoding the prepro-region of a preprosomatostatin and a heterologous polypeptide α-globin, when transfecting cells with said vector, "mature" α-globin was produced by these cells (the abstract, and page 1648, the right column), and that the chimeric polypeptide was recognized by the processing enzymes nearly as efficiently as native preprosomatostatin (page 1652, the left column), indicating the role of the pro-region of preprosomatostatin in targeting a peptide to regulated secretory pathway.

Habener teaches that GLP-1 (like somatostatin) is a peptide hormone and generated from a prohormone precursor proglucagon (column 2, lines 16-22), and that GLP-1 has insulinotropic activity, and a potential therapeutic use for diabetes mellitus (the abstract).

Suzuki teaches that it is desirable in the art to utilize the expression of a chimeric protein for a number of peptide production, and that enzymatic cleavage can be used for separating a target peptide (column 1, lines 15-18). Further, Suzuki teaches a construct for the expression of a chimeric peptide such as peptide hormones including GLP-1 (column 5, lines 13-22). Additionally, Suzuki teaches that when a peptide hormone or a precursor thereof is produced in an organism, a precursor polypeptide for the peptide is specifically cleaved by a processing enzyme such as prohormone enzyme PC1/3 and furin, and that when these processing enzymes are used for excising a target peptide from the chemeric protein, it is expected that the peptide hormone is not damaged and the processing enzyme is applicable to a wide variety of peptides, therefore, the development of such production methods has been desired in the art (column 1, lines 36-49).

Patel teaches that the mammalian pro-protein convertases comprise furin, PACE4 and PC1-6, which mediate endoproteolysis of prohormone precursors, and that furin is capable of monobasic processing prohormone precursors, such as prosomatostatin (the abstract).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a construct and a host cell thereof for the purpose of expressing a small hormone peptide such as GLP-1, wherein the construct comprises the nucleic sequences encoding pre- pro- regions of preprosomatostatin, a furin cleavage site, and GLP-1 as taught by Sevarino and Stoller that the pro-region of preprosomatostatin can be used for targeting a heterologous peptide to regulated secretory pathway, and by Suzuki that a chimeric prohormone of GLP-1 can be cleaved to produce the mature hormone peptide by processing enzymes such as furin. The person of ordinary skill in the art would have been motivated to make the construct and the host cell for expressing GLP-1 because of the potential therapeutic application of GLP-1 in treating diabetes as suggested by Habener, the advantage of using the pro-region of prosomatostatin in targeting the hormone peptide as taught by Sevarino and Stoller, and the advantage of using the prohormone processing enzymes such as furin for cleaving the chimeric peptide in order to remain the peptide undamaged as taught by Suzuki, and reasonably would have expected success because Sevarino and Stoller have demonstrated successful expression of two different heterologous peptides by using fusing pro-region of

prosomatostatin with the target peptide, and the prior art has established that when a processing enzyme such as furin is used for excising a target peptide from the chemeric protein, the peptide hormone is not damaged, as indicated by Suzuki.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Gerich et al. (Diabetes, 1976, 25 (suppl. 1): 340) discloses a method for treating human diabetes using somatostatin plus insulin, and indicates that such therapy is more effective than insulin alone in the treatment of diabetes (the abstract, the last three lines).

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 703-305-1345. The examiner can normally be reached on Monday - Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

LORRAINE SPECTOR
PRIMARY EXAMINER

Dong Jiang, Ph.D.
Patent Examiner
AU1646
12/4/02